EXHIBIT 1b

increased risk of ADHD in offspring associated with both maternal and paternal psychiatric disorder, including both ADHD and other psychiatric disorders such as ASD, Major Depressive Disorder (MDD), and bipolar disorder (BD).[172] The study enrolled over 4,000,000 children born in Taiwan and accessed medical record diagnoses for parents and their offspring. Offspring of parents with ADHD had a higher risk for ADHD than controls (HR 45.12, 95% CI 38.57, 52.78). Maternal ADHD conferred a nearly 30-fold increased risk for offspring ADHD (OR 29.38, 95% CI 27.63, 31.25), and paternal ADHD conferred a 19-fold increase (OR 19.02, 95% CI 16.98, 21.38).

In addition, the Liang et al. 2021 study authors noted that children of parents with Major Depressive Disorder have been reported as having a 4.35-fold risk of developing conduct disorder/ADHD (range of OR: 1.59–10.78). Liang et al. 2021 concluded that maternal ASD was associated with a higher offspring risk for ADHD (OR 4.34, 95% CI 2.89–6.51), maternal Major Depressive Disorder was associated with a higher offspring risk for ADHD (OR 1.97, 95% CI 1.92–2.03), and maternal BD bipolar disorder was associated with a higher risk for ADHD (1.44, 95% CI 1.37–1.52).

3. Infection/Fever

A recent paper by Walle et al. 2022 assessed the risk of ADHD due to prenatal exposure to maternal infection accompanied by fever. Increased ADHD risk was observed after exposure to genitourinary infections in the second trimester (OR = 1.42, 95% CI 1.06–1.90) or third trimester (OR = 2.04, 95% CI 1.9–3.49), and to respiratory infections in the second trimester (OR = 1.31, 95% CI 1.12–1.54), when the infections were accompanied by fever. However, the authors noted that the association between infection and ADHD should be estimated using discordant siblings or a negative control design to better adjust for unmeasured familial confounding.

Similarly, Gustavson et al. 2019 assessed the risk of ADHD due to prenatal exposure to maternal fever. Increased ADHD risk was observed after exposure to fever in the first trimester (OR = 1.31, 95% CI 1.06–1.61). The risk increased for children exposed twice or more to fever in the first trimester (OR = 2.64, 95% CI 1.36–5.14). The risk of receiving an ADHD diagnosis

[172] Liang CS, Bai YM, Hsu JW, Huang KL, Ko NY, Yeh TC, Chu HT, Tsai SJ, Chen TJ, Chen MH. Associations of parental mental disorders and age with childhood mental disorders: a population-based cohort study with four million offspring. Eur Child Adolesc Psychiatry. 2023 May;32(5):825-833. doi: 10.1007/s00787-021-01914-3. Epub 2021 Nov 21. PMID: 34802066.

was similar regardless of whether the mother took acetaminophen (OR = 1.32, 95% CI 1.01, 1.71) or did not take acetaminophen (OR = 1.35, 95% CI 0.96, 1.90).

4. Prenatal And Obstetric Factors

Both maternal hypertension (25% increase in risk) and preeclampsia (15-40% increase) have been linked to ADHD.[173] Several large studies report an increased risk of ADHD (50-60%) among offspring of obese mothers.[174] In addition, there is a growing body of literature on the impact of stress during pregnancy on the risk of ADHD in offspring, including a report of a two-fold increase among mothers who experienced a death in the family.[175] Notably, these results differ from the results of Danish national registry study, discussed above, which suggested no association between maternal bereavement and the separate disorder of ASD.[176]

Silva et al. 2014 reports on a number of pregnancy/labor factors associated with ADHD, including maternal urinary tract infection, preeclampsia, induced labor, cord prolapse and threatened pre-term labor. However, in Silva et al. 2014, when maternal smoking was entered into the model, almost all other relationships became attenuated. While these factors should be

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[173] Maher GM, O'Keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, Khashan AS. Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2018 Aug 1;75(8):809-819. doi: 10.1001/jamapsychiatry.2018.0854. PMID: 29874359; PMCID: PMC6143097.

Maher GM, Dalman C, O'Keeffe GW, Kearney PM, McCarthy FP, Kenny LC, Khashan AS. Association between preeclampsia and attention-deficit hyperactivity disorder: a population-based and sibling-matched cohort study. Acta Psychiatr Scand. 2020 Oct;142(4):275-283. doi: 10.1111/acps.13162. Epub 2020 Feb 29. PMID: 32056200.

[174] Jenabi E, Bashirian S, Khazaei S, Basiri Z. The maternal prepregnancy body mass index and the risk of attention deficit hyperactivity disorder among children and adolescents: a systematic review and meta-analysis. Korean J Pediatr. 2019 Oct;62(10):374-379. doi: 10.3345/kjp.2019.00185. Epub 2019 Jun 14. PMID: 31208166; PMCID: PMC6801198.

Sanchez CE, Barry C, Sabhlok A, Russell K, Majors A, Kollins SH, Fuemmeler BF. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes Rev. 2018 Apr;19(4):464-484. doi: 10.1111/obr.12643. Epub 2017 Nov 22. PMID: 29164765; PMCID: PMC6059608.

Andersen CH, Thomsen PH, Nohr EA, Lemcke S. Maternal body mass index before pregnancy as a risk factor for ADHD and autism in children. Eur Child Adolesc Psychiatry. 2018 Feb;27(2):139-148. doi: 10.1007/s00787-017-1027-6. Epub 2017 Jul 15. PMID: 28712019.

[175] Hartman C.A., Rommelse N., Van Der Klugt C.L., Wanders R.B., Timmerman M.E. Stress Exposure and the Course of ADHD from Childhood to Young Adulthood: Comorbid Severe Emotion Dysregulation or Mood and Anxiety Problems. J. Clin. Med. 2019;8:1824;

Saccaro LF, Schilliger Z, Perroud N, Piguet C. Inflammation, Anxiety, and Stress in Attention-Deficit/Hyperactivity Disorder Published online 2021 Sep 24.

[176] Li J, Vestergaard M, Obel C, Christensen J, Precht DH, Lu M, Olsen J. A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. Pediatrics 2009;123: 1102–1107.

considered when designing epidemiological studies, additional research is required before determining such exposures are risk factors.

5. Parental Age

Most large cohort studies report younger paternal or maternal ages being associated with an increased risk of ADHD in the offspring, but some studies also report an increased risk in older fathers.[177] D'Onofrio et al. 2014 reported that, compared with offspring born to fathers 20 to 24 years old, offspring of fathers older than 45 had a substantial, albeit imprecise, increase in the risk of ADHD (HR = 13.13, 95% CI 6.85-25.16).[178]

6. Low Birthweight And Gestational Age

The literature supports an association between low birthweight and pre-term birth and an increased risk of ADHD. Low birthweight, categorized as <2500g (approximately 5.5 pounds) and pre-term birth of <33 weeks gestation, has been repeatedly linked to an increased risk of ADHD. A recent meta-analysis with over 6,000 participants reported a three-fold increase in ADHD among babies born pre-term or low birthweight.[179] The meta-analysis reviewed 12 studies and reported that the risk of ADHD is doubled for those born very pre-term (less than 32 weeks gestation) or very low birthweight (defined as <1,500g (approximately 3.3 pounds)) (OR = 2.25, 95% CI 1.56 to 3.26) and quadrupled for those born extremely pre-term (<28 weeks gestation) or extremely low birthweight (defined as <1,000g (approximately 2.2 pounds)) (OR = 4.05, 95% CI 2.38 to 6.87). Song et al. used data from the Korean National Health Insurance database and reported that infants with birthweights of 2.0–2.4 kg (approximately 4.4-5.3 pounds) had an adjusted OR = 1.41 (95% CI 1.33, 1.50) and those with birthweights of 1.5–1.9 kg (approximately

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[177] Chudal R, Joelsson P, Gyllenberg D, Lehti V, Leivonen S, Hinkka-Yli-Salomaki S, Gissler M, Sourander A (2015) Parental age and the risk of attention deficit hyperactivity disorder: a nationwide, population-based cohort study. J Am Acad Child Adolesc Psychiatry 54(6):487–494.

Janecka M, Hansen SN, Modabbernia A, Browne HA, Buxbaum (2019) Parental age and differential estimates of risk for neuropsychiatric disorders: findings from the Danish birth cohort. J Am Acad Child Adolesc Psychiatry 58(6):618–627.

de Kluiver H, Buizer-Voskamp JE,Dolan CV, Boomsma DI. 2017. Paternal Age and Psychiatric Disorders: A Review. Am J Med Genet Part B 174B:202–213.

McGrath JJ, Petersen L, Agerbo E, Mors O, Mortensen PB, Pedersen CB (2014) A comprehensive assessment of parental age and psychiatric disorders. JAMA Psychiat 71(3):301–309.

[178] D'Onofrio BM, Rickert ME, Frans E, Kuja-Halkola R, Almqvist C, Sjölander A, et al.Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 2014;71(4):432–8.

[179] Franz AP, Bolat GU, Bolat H, et al. Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. Pediatrics.2018;141(1):e20171645.

3.3 -4.2 pounds) had an adjusted OR = 1.49 (95% CI 1.33-1.66), and were at increased risk of ADHD, controlling for congenital or perinatal diseases.[180] Other large cohort studies support this finding (Halmoy et al. 2012; Henriksen et al. 2015; Silva et al. 2014), although Silva showed an attenuation of risk when controlling for maternal smoking, something that the other two studies lacked the data to do.[181]

Additionally, Lindstrom et al. 2018 reported a stepwise increase in the risk of ADHD with increasing degree of prematurity in Sweden. Similar results were reported in Finland.[182]

It is important to point out the possibility that the risk of low birthweight or pre-term birth and the risk of ADHD are both linked to an underlying genetic risk, something that few studies have the ability to fully adjust for or address.

7. Smoking

Several studies implicate prenatal smoking as a risk factor for offspring ADHD.[183] However, those studies that controlled for confounding by genetic/familial factors show an attenuation of that risk, often completely eliminating it. For example, a large cohort study from Sweden demonstrated an attenuation of the risk of heavy smoking on ADHD from HR = 2.5 (95%

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[180] Song IG, Kim HS, Cho YM, Lim YN, Moon DS, Shin SH, Kim EK, Park J, Shin JE, Han J, Eun HS. Association between birth weight and neurodevelopmental disorders assessed using the Korean National Health Insurance Service claims data. Sci Rep. 2022 Feb 8;12(1):2080. doi: 10.1038/s41598-022-06094-x. PMID: 35136157; PMCID: PMC8827104.

[181] Halmøy A, Klungsøyr K, Skjærven R, Haavik J. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2012;71(5):474–81.

Henriksen L, Wu CS, Secher NJ, Obel C, Juhl M. Medical augmentation of labor and the risk of ADHD in offspring: a population based study. Pediatrics. 2015;135(3):e672–7;

Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. Pediatrics. 2014;133(1):e14–.

[182] Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelsson P, Gissler M, Sourander A. Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/ Hyperactivity Disorder. Pediatrics. 2015 Sep;136(3):e599-608. doi: 10.1542/peds.2015-1043. PMID: 26304830.

[183] Langley K, Heron J, Smith GD, Thapar A. Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. Am J Epidemiol. 2012;176(3):261–8

Thakur GA, Sengupta SM, Grizenko N, Schmitz N, Pagé V, Joober R. Maternal smoking during pregnancy and ADHD: a comprehensive clinical and neurocognitive characterization. NicotineTob Res. 2013;15(1):149–57;

Biederman J, Petty CR, Bhide PG, Woodworth KY, Faraone S. Does exposure to maternal smoking during pregnancy affect the clinical features of ADHD? Results from a controlled study. World J Biol Psychiatry. 2012;13(1):60–4;

Sengupta SM, Fortier MÈ, Thakur GA, Bhat V, Grizenko N, Joober R. Parental psychopathology in families of children with attention deficit/ hyperactivity disorder and exposed to maternal smoking during pregnancy. J Child Psychol Psychiatry. 2015;56(2):122–9.

CI 2.4-2.6) to HR=1.89 (95% CI 1.83, 1.97) with use of cousin controls, and a complete reduction to the null with use of sibling controls, which indicated HR = 0.84 (95% CI 0.65-1.06).[184]

8. Exogenous Chemicals And Environmental Contaminants

There are limited data on the impact of prenatal exposure to chemicals or environmental contaminants on the risk of ADHD, although an association with prenatal exposure to the anti-epileptic drug valproate is supported by data.[185]

Regarding valproate exposure, a 50% increased risk of ADHD was reported among children prenatally exposed to the medication.[186] However, a meta-analysis (Veroniki et al. 2019) assessed a range of adverse neurodevelopmental outcomes, including ASD and ADHD, and failed to support a significant association between prenatal exposure to valproate and childhood ADHD, although it did report an association for ASD. The ADHD analysis included 5 cohort studies assessing both prenatal exposure and exposure through breastfeeding. The authors caution that the results of the meta-analysis "should be interpreted with caution, as a number of factors (e.g., anticonvulsant dosing, severity of epilepsy, duration of exposure, serum concentrations of exposure, mother's IQ/education) that may all influence outcomes were not identified."

[184] Skoglund C, Chen Q, D'Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. J Child Psychol Psychiatry. 2014;55(1):61–8.

[185] Christensen J, Pederson L, Sun y et al. Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring JAMA Network Open. 2019;2(1):e186606.

Wiggs KK, Rickert ME, Hernandez-Diaz S, Bateman BT, Almqvist C, Larsson H, Lichtenstein P, Oberg AS, D'Onofrio BM. A Family-Based Study of the Association Between Labor Induction and Offspring Attention-Deficit Hyperactivity Disorder and Low Academic Achievement. Behav Genet. 2017 Jul;47(4):383-393. doi: 10.1007/s10519-017-9852-4. Epub 2017 May 27. PMID: 28551761.

[186] Christensen J, Pederson L, Sun y et al. Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring JAMA Network Open. 2019;2(1):e186606.

see also Wiggs KK, Rickert ME, Hernandez-Diaz S, Bateman BT, Almqvist C, Larsson H, Lichtenstein P, Oberg AS, D'Onofrio BM. A Family-Based Study of the Association Between Labor Induction and Offspring Attention-Deficit Hyperactivity Disorder and Low Academic Achievement. Behav Genet. 2017 Jul;47(4):383-393. doi: 10.1007/s10519-017-9852-4. Epub 2017 May 27. PMID: 28551761.

B. Overview Of Epidemiological Data Addressing Prenatal Exposure To Acetaminophen And ADHD

1. Studies Investigating Potential Association Between Maternal Acetaminophen Use And ADHD Diagnosis

Only a small number of studies have addressed the potential association between maternal acetaminophen use during pregnancy and a subsequent clinical diagnosis of ADHD in offspring. These studies do not support a causal inference because they generally showed very low associations, and the one study with sibling controls showed no association at all.

Study	Population	Exposure Measurement	Outcomes Tested	Results
Gustavson et al. 2021	21,448 children	Material report at 18 & 30 weeks of pregnancy and six months post-partum	ADHD	1-7 days aHR = 0.87, 95% CI 0.70, 1.08
				8-28 days aHR = 1.13, 95% CI 0.82, 1.49
				> 29 days aHR= 2.02 95% CI 1.17–3.25 and sibling controlled aHR=1.06 95% CI 0.51-2.05
Ystrom et al. 2017	112,973 children and their parents	Maternal report at 18 & 30 weeks of pregnancy and six months post-partum; duration of exposure divided by trimester; duration also divided by number of days; usage for fever and infection	ADHD	One trimester HR=1.07, 95% CI 0.96-1.19
				Two trimesters (HR = 1.22, 95% CI 1.07, 1.38)
				Three trimesters (HR=1.27, 95% CI 0.99-1.63)
				>29 days (HR=2.20, 95% CI 1.50-3.24)
				<8 days (HR=0.90, 95% CI 0.81-1.00)

Study	Population	Exposure Measurement	Outcomes Tested	Results
				Use for infections (HR=6.15, 95% CI 1.71-22.05)
Ji et al. 2018	1,180 mother/infant pairs	APAP biomarkers in maternal plasma	ADHD, ASD	Acetaminophen Burden OR=1.88, 95% CI 1.18, 3.00
Ji et al. 2020	996 children	APAP metabolites in cord plasma and maternal plasma	ADHD, ASD	ADHD Diagnosis 2nd Tertile: OR=2.26, 95% CI 1.40, 3.69 ADHD Diagnosis 3rd Tertile OR=2.86 95% CI 1.77, 4.67
Anand et al. 2021	3,165 mother-child pairs; 568 with cord plasma data	APAP metabolites in cord plasma and maternal plasma	ADHD	APAP >50th percentile aOR=2.10 95% CI 1.43, 3.11
Liew et al. 2014	64,322 mother-child pairs	Maternal re-report at 12 & 30 weeks and 6 months post-partum	SDQ, Hyperkinetic Disorder Diagnosis, ADHD Prescriptions	SDQ aRR=1.13, 95% CI 1.01, 1.27 HKD aHR=1.37, 95% CI 1.19, 1.59 ADHD prescriptions (aHR=1.29, 95% CI 1.15, 1.44)
Baker et al. 2020	345 children	APAP metabolites from meconium	ADHD	OR-2.43, 95% CI 1.41, 4.21
Liew et al. 2019	116,430 females	Questionnaire on APAP use	ADHD	OR=1.34, 95% CI 1.05, 1.72
Gustavson et al. 2019	114,739 children from Norwegian Mother and Child Cohort Study	Maternal self-report	ADHD	Risk associated with fever (aOR: 1.30, 1.15-1.47) unchanged when treated with acetaminophen.

a. Results Of Cohort Studies

Gustavson et al. 2021.[187] In this study, researchers obtained data from the Norwegian Mother and Child Cohort (MoBa) and the Norwegian Patient Registry to assess a potential association between maternal acetaminophen use during pregnancy and a diagnosis of ADHD. This study is unique because the authors conducted a sibling-control design to test the impact of potential unmeasured maternal/familial confounding factors on the association between maternal acetaminophen use during pregnancy and child ADHD diagnosis. Because more children in the MoBa cohort had outcome data available at the time of this analysis, the researchers were able to compare the outcome of ADHD diagnosis in siblings from the same family with differential exposure to acetaminophen. In other words, researchers compared outcomes for siblings whose mothers used acetaminophen during one pregnancy but not during another pregnancy.

The cohort recruited a total of 112,762 women and collected data from a total of 114,479 children between 1999 and 2008. Exposure data were obtained through maternal report. After initial adjustments, the authors reported that children exposed to acetaminophen up to 28 days during pregnancy were not at an increased risk of ADHD diagnosis compared to unexposed children. Specifically, the data showed that children whose mothers used acetaminophen for 1-7 days had no increased risk of ADHD diagnosis (aHR = 0.87, 95% CI 0.70, 1.08) and children whose mothers used acetaminophen for 8-28 days likewise had no increased risk of ADHD diagnosis (aHR = 1.13, 95% CI 0.82, 1.49). Although long-term exposure (29 days or more) prior to adjustment was associated with a two-fold increase in risk of ADHD diagnosis (aHR = 2.02, 95% CI 1.17, 3.25), this increase was attenuated after the authors performed the analysis using sibling control to address potential confounding from genetic factors (aHR = 1.06, 95% CI 0.51, 2.05).

Ystrom et al. 2017[188] is a prior study using the same cohort and likewise reported no association with an increased risk of an ADHD diagnosis for children whose mothers used acetaminophen for less than 28 days. The authors adjusted for maternal use of acetaminophen

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[187] Gustavson K, Ystrom E, Ask H, et al. Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder – a longitudinal sibling control study. JCPP Adv. 2021;1(2). doi:10.1002/jcv2.12020.

[188] Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

before pregnancy, familial risk for ADHD, and indications of acetaminophen use. The authors attempt to establish a dose response by calculating a Hazard Ratio (HR) based on the number of trimesters of exposure and by assessing the number of days acetaminophen use was reported by the mother. As to the analysis by trimester, in the fully adjusted model, the authors report the association between any prenatal maternal use of acetaminophen as follows:

- one trimester: HR = 1.07, 95% CI 0.96, 1.19
- two trimesters: HR = 1.22, 95% CI 1.07, 1.38
- three trimesters: HR = 1.27, 95% CI 0.99, 1.63

These results do not support a dose-response relationship because statistical significance is only achieved for two trimesters of exposure but not for one or three trimesters of exposure.

With regard to the analysis based on the number of days of acetaminophen use reported by the mother, the authors report a HR of 2.20 (95% CI 1.50, 3.24) with ADHD when acetaminophen was used during pregnancy for more than 29 days. When acetaminophen was used during pregnancy for <8 days, there was no association with ADHD (HR = 0.90, 95% CI 0.81, 1.00).

The authors also report that acetaminophen use for fever and infections for 22 to 28 days was associated with ADHD (HR = 6.15, 95% CI 1.71, 22.05). This elevated HR associated with fever and infection, although imprecise, supports the hypothesis that underlying infection and fever (confounding by indication) may be driving the observed increase in risk.

The authors also present data using what they describe as negative controls. The first is paternal acetaminophen use six months before pregnancy. The study found that paternal use of acetaminophen six months before pregnancy was associated with offspring ADHD:

- 1-7 days use: HR = 1.10, 95% CI 0.92, 1.30
- 8-28 days use: HR = 1.81, 95% CI 1.26, 280
- 29 or more days use: HR = 2.06, 95% CI 1.36, 3.13

These results are clear evidence that residual confounding is present. While the study also used pre-pregnancy maternal use of acetaminophen as a "so-called" negative control, that is an inadequate way to address concerns about confounding, as discussed in Section V.B., above.

Ji et al. 2018 and ***Ji et al. 2020*** are two studies that utilized data from the Boston Birth Cohort (BBC),[189] as discussed in Section VI.B.1, above, and measured acetaminophen metabolites in maternal plasma and cord blood as a basis to evaluate the child's exposure to acetaminophen from maternal use.[190]

In Ji et al. 2018, the authors analyzed maternal plasma biomarkers in 1,180 children enrolled at birth and reported a significant positive dose-response association with ADHD diagnosis for each maternal acetaminophen biomarker, which persisted after adjusting for indication of acetaminophen use and other pertinent covariates. Although the authors lacked data on the actual dose of acetaminophen ingested or passed to the offspring in utero, the analysis separated acetaminophen exposure into tertiles and also compared exposure above and below the median. The risk ratios for ADHD reported in the fully adjusted model analyzing acetaminophen burden below median were 1.58 (95% CI 1.02, 2.46) and above median were 1.88 (95% CI 1.18, 3.00).

In Ji et al. 2020, the authors analyzed data from BBC participants, including 257 children (25.8%) with ADHD only, 66 (6.6%) with ASD only, 42 (4.2%) with both ADHD and ASD, 304 (30.5%) with other developmental disabilities, and 327 (32.8%) who were neurotypical. The authors reported that compared with being in the first tertile, being in the second and third tertiles of cord acetaminophen burden was associated with higher odds of ADHD diagnosis (2nd tertile OR = 2.26, 95% CI, 1.40, 3.69) (3rd tertile OR = 2.86, 95% CI 1.77, 4.67). They reported consistent associations between acetaminophen burden and ADHD across strata of potential confounders, including maternal indication, substance use, pre-term birth, and child age and sex.

Dr. Baccarelli states in his report that cord blood measurements are more accurate than maternal reports of acetaminophen use because they are objective. But this assertion ignores the

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[189] Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. Brain Sci. 2018;8(127):15. doi:doi:10.3390/brainsci8070127.

Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

[190] Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. Brain Sci. 2018;8(127):15. doi:doi:10.3390/brainsci8070127.

Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

fact, as elaborated in Section VI.B.1 above, that the measurement of acetaminophen metabolites in cord blood represents a single moment in time immediately prior to delivery. Because the half-life of acetaminophen is 1.5-3 hours, the cord blood and cord plasma measurements represent exposure shortly before delivery and are inadequate to measure maternal use and fetal exposure throughout pregnancy. In particular, it is impossible to determine whether the exposure happened during critical periods of brain development, throughout gestation, or simply as a result of maternal acetaminophen use during labor specifically. As such, the adjusted odds ratios reported by the authors, although statistically significant, provide little to no value in evaluating whether acetaminophen exposure during pregnancy generally is causally related to ADHD diagnosis in offspring. Additionally, how the "tertiles" used by the authors correlate to actual dose is unquantifiable, and, critically, there was no adjustment for genetic/familial factors in either study.

Anand et al. 2021[191] also assessed mother-child cord-blood data from the BBC. ADHD was identified in 248 children (43.7%), while 320 children (56.3%) had neurotypical development. The authors reported that children with cord acetaminophen >50th percentile had significantly higher odds of ADHD when cord levels of 8-hydroxy-deoxyguanosine (described by the authors as an "oxidative stress biomarker") were ≤50th percentile (OR = 2.21, 95% CI 1.37, 3.58), and even higher odds when 8-hydroxy-deoxyguanosine was >50th percentile (OR = 2.38, 95% CI 1.49, 3.82). But the results of the study are difficult to interpret, as it appears that the risk increases at the top 50th percentile as well as the bottom 50th percentile, calling into question whether the oxidative stress biomarker rather than acetaminophen is driving the results (and correspondingly whether oxidate stress correlates to acetaminophen use). The authors also noted that these findings are in opposition to their original hypothesis that lower levels of amino acids involved in the synthesis of glutathione, the antioxidant that detoxifies one of the acetaminophen metabolites (i.e., a substance formed during the metabolism of acetaminophen), may explain the association between cord acetaminophen and ADHD risk.

Notably, levels of glutathione in the cord blood were not available in the database. In addition, as with Ji et al. 2018 and Ji et al. 2020, the cord plasma measurements captured only a snapshot of fetal metabolism at the time of birth and therefore do not reveal anything about

[191] Anand NS, Raghavan R, Wang G, Hong X, Azuine RE, Pearson C, Zuckerman B, Xie H, Wang X. Perinatal Acetaminophen Exposure and Childhood Attention-Deficit/Hyperactivity Disorder (ADHD): Exploring the Role of Umbilical Cord Plasma Metabolites in Oxidative Stress Pathways. Brain Sci. 2021 Sep 30;11(10):1302. doi: 10.3390/brainsci11101302. PMID: 34679367; PMCID: PMC8533963.

acetaminophen exposure during earlier stages of pregnancy. Indeed, the authors pointed out that they do not have sufficient information to correlate cord acetaminophen intensities to dosage and frequency of maternal acetaminophen use during pregnancy.

Baker et al. 2020[192] utilized data from the GEST cohort and measured acetaminophen in meconium (a newborn's first bowel movement) in 345 children from a cohort in Sherbrooke, Quebec, Canada. The study recorded information on ADHD diagnosis at 6-7 years (by a physician or from medical records) and hyperactivity using the Behavioral Assessment System (parent report). Meconium acetaminophen was present in 57.7% of participants and was categorized as none (<50th percentile of exposure) or high. No information on timing of exposure was available. The authors reported an elevated risk associated with detection of any meconium acetaminophen (OR = 2.43, 95% CI 1.41, 4.21) and a marginally elevated dose response (OR = 1.10, 95% CI 1.02, 1.19). They modeled meconium acetaminophen as a continuous variable and report that for each doubling of exposure, there was a 10% increase in the odds of ADHD.

It is unclear what the levels of acetaminophen in meconium mean in terms of dose and timing of exposure to a developing fetus. Additionally, the acetaminophen levels in meconium were not correlated to maternal recall of acetaminophen use.

The authors acknowledge the importance of familial factors/genetics, noting that they sought to adjust for maternal ADHD but were unable to do so due to insufficient data. As a result, this study raises serious concerns about confounding by familial/genetic risk.

The authors also reported the results of magnetic resonance imaging (MRI) for 48 of the study participants at ages 9-11. In this exploratory analysis, they reported a correlation between acetaminophen exposure and changes in neuronal connectivity. In the absence of a control group of unexposed children, however, it is impossible to interpret this finding. Additionally, MRI analysis identified only an association between resting state connectivity and hyperactivity in this small sample of children. A statistically significant association was not identified for attention problems.

In his report, Dr. Baccarelli repeatedly states that a strength of this study, of which he is an author, is the biologic marker of acetaminophen, coupled with a diagnosis for ADHD in youth and

[192] Baker BH, Lugo-Candelas C, Wu H, et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity. JAMA Pediatr. 2020;174(11):1073-1081. doi:10.1001/jamapediatrics.2020.3080.

the use of a brain MRI to assess brain function in the children. His report claims that the limited sample size (only 345 children) is mediated by the added precision of meconium and mechanistic support in the form of brain MRI measurements performed on study participants.[193] As a result, Dr. Baccarelli states that methodology utilized in the study is likely "the strongest in the literature."[194]

Dr. Baccarelli's analysis of this study ignores its numerous and significant weaknesses. First, because meconium is collected after delivery, it potentially includes acetaminophen from exposure during or after labor (e.g., through breastfeeding or acetaminophen administered to a newborn). Additionally, plaintiffs' expert Dr. Cabrera acknowledges "the possibility that meconium may not accurately reflect prenatal acetaminophen exposure."[195] Second, Dr. Baccarelli's report provides the sample size of children who had meconium collected, but the report does not include the fact that MRIs—which Dr. Baccarelli asserts are critical to validating the study despite its small sample size—were performed on only 48 of those children.[196] And while the MRIs performed on a small subset of the study population assessed connectivity in multiple classical brain networks, a statistically significant association was never identified for those subjects with attention problems, which is a diagnostic criterion of ADHD pursuant to the DSM-V.[197] Finally, the increased odds of a diagnosis of ADHD when acetaminophen is detected in meconium had a wide confidence interval (OR = 2.43, 95% CI 1.41, 4.21) rendering the finding imprecise.[198] And while the authors claim that the study shows a dose-response association, (OR = 1.10, 95% CI 1.02, 1.19) it is likely the result of residual confounding as the study did not adjust for genetics or confounding by indication.

[193] Baccarelli Appendix at p. 1.

[194] Baccarelli Rep. at 91.

[195] Cabrera Rep. at 138.

[196] Baccarelli Rep. at 89; Baker et al. 2020.

[197] DSM-V and supplemental table.

[198] Baker BH, Lugo-Candelas C, Wu H, et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity. JAMA Pediatr. 2020;174(11):1073-1081. doi:10.1001/jamapediatrics.2020.3080.

Liew et al. 2014[199] analyzes 64,322 mother-child pairs from the Danish National Birth Cohort and reports that children whose mothers used acetaminophen during pregnancy were at higher risk for a hospital diagnosis of hyperkinetic disorder (HKD) (HR = 1.37, 95% CI 1.19, 1.59), use of ADHD medications (HR = 1.29, 95% CI 1.15, 1.44), or ADHD-like behaviors at age 7 (RR = 1.13, 95% CI 1.01, 1.27). Outcomes were assessed through:

- Parental reports of behavioral problems in children age 7 using the Strengths and Difficulties Questionnaire (SDQ);
- Retrieved hyperkinetic disorder diagnoses (HKD) from the Danish National Hospital Registry or the Danish Psychiatric Central Registry prior to 2011; and
- Identified ADHD prescriptions (mainly Ritalin) for children from the Danish Prescription Registry.

The authors reported stronger associations with acetaminophen use in more than one trimester during pregnancy, but the results are inconsistent. For results on the SDQ, only one combination of trimesters (2nd and 3rd) yields a significant OR (1.44, 95% CI 1.12, 1.87). The OR for all three trimesters, however, is lower (OR = 1.24, 95% CI 1.03, 1.48). The authors reported an increase in risk over weeks of acetaminophen use, but the ORs are all non-significant until the category of >28 weeks (OR = 1.46, 95% CI 1.16, 1.85).

Although a somewhat more robust pattern of dose-response is seen when the risk was assessed by trimester and weeks of use for the other two outcomes, HKD and ADHD medication prescription, there are still inconsistencies in the patterns of ORs presented and the overlapping confidence intervals raise the question of whether the values are meaningfully different. The authors report a significant p-value for trend, a test of the hypothesis of an ordered relationship across the range of a predictor variable. But there is debate about whether this test should be used in assessing data where non-significant results have already been found. In such circumstances, it could be seen as "massaging" the data or "fishing" for a significant effect. As Gibbs and Gibbs 2015 state: "[t]o be consistent, either all ***p*** values within this hypothetical range suggest or support

[199] Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

a trend or none. Describing some 'almost significant' ***p*** values as a trend but not others introduces a large element of subjectivity."[200]

Close examination of the results presented in this paper makes it clear that there are inconsistencies across the range of exposure levels, whether calculated by trimester or by weeks of exposure. One must, therefore, question the decision to report a p-value for trend. Moreover, the authors of this study simultaneously tested multiple different hypotheses based on exposure level and trimester of acetaminophen usage. As noted above, there is an increased risk of study error where multiple sets of hypotheses are tested simultaneously, and epidemiologists commonly account for the probability of these errors by, for example, conducting a multiple testing adjustment analysis (or multiplicity analysis). The failure to do so here could have affected the overall significance finding or the p-value given the large number of ORs calculated.

In addition, although acetaminophen use was ascertained using interviews throughout pregnancy, maternal report of acetaminophen use can nonetheless suffer from reporting bias, rendering exposure misclassification possible. In fact, the authors report that information on dosing was not included because women reported that they could not recall how many pills they took, and 28% of mothers who reported acetaminophen use were unable to specify the gestational week of use. This could either artificially inflate or reduce any reported association with outcome, depending on the direction of the misclassification. Results did not appear to be confounded by maternal inflammation, infection during pregnancy, or the mother's mental health problems, but residual confounding due to familial and genetic factors are still a concern.

Five years after this study, these same authors published a study using the Nurses' Health Study II cohort (NHS II), ***Liew et al. 2019***, which obtained ADHD diagnosis through maternal report. NHS II is a longitudinal cohort study of 116,430 female nurses age 25-42 years recruited in 1989 and followed up biennially every odd calendar year. Questionnaires ask nurses who are mothers to report whether they used acetaminophen regularly (defined as ≥2 times/week in the 1989 and 1993 questionnaires and ≥1 day/week from 1995 onwards) during the previous two years. Regular maternal acetaminophen use (yes/no) reported on the questionnaire during the year of the

[200] Gibbs NM, Gibbs SV. Misuse of 'trend' to describe 'almost significant' differences in anaesthesia research. Br J Anaesth. 2015 Sep;115(3):337-9. doi: 10.1093/bja/aev149. Epub 2015 May 29. PMID: 2602523.

child's birth was analyzed as the exposure variable of interest and is referred to as use "at the time of pregnancy."[201] However, this question was not about use specifically during pregnancy.

A total of 721 children (8.1%) in the cohort had been diagnosed with ADHD as reported by the mothers. A purported negative control exposure (NCE) was performed using two NCE periods (about four years before and four years after pregnancy). The analysis suggested that only acetaminophen use during pregnancy was associated with childhood ADHD (OR = 1.34, 95% CI 1.05, 1.72), and the effect estimates for the two NCE periods were null, but as discussed above, negative control analysis using data on pre- and post-pregnancy use of acetaminophen is not valid.

Critically, this cohort was not limited to pregnant women. Therefore, information on the regular usage of acetaminophen was not specific to pregnancy. The authors assumed that if the mothers gave birth in the same year they filled out the survey, the regular usage would have continued throughout pregnancy. The authors note that "we expect that the nurse mothers who indicated regular acetaminophen use in the questionnaires would likely have taken acetaminophen during pregnancy."[202] Such imperfect exposure assessment cannot be relied upon when the opportunity for misclassification is so high. And even based on this improper assumption, the authors reported only a very small association of acetaminophen use during pregnancy with borderline statistical significance (aOR 1.46, 95% CI 1.01, 2.09).

One study, ***Gustavson et al. 2019***,[203] evaluated whether the association between maternal fever and ADHD among offspring was affected by acetaminophen use to treat fever. This study did not directly measure the association between maternal use of acetaminophen and childhood ADHD. In this study, maternal fever was associated with a slightly increased risk of ASD (aOR=1.30, 95% CI 1.15, 1.47). For children exposed to fever in the first trimester (aOR=1.31, 95% CI 1.06, 1.61), the association doubled for two or more fevers (aOR =2.64, 95% CI 1.36,

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[201] Liew Z, Kioumourtzoglou MA, Roberts AL, O'Reilly ÉJ, Ascherio A, Weisskopf MG. Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. Am J Epidemiol. 2019;188(4):768-775. doi:10.1093/aje/kwy288.

[202] Liew Z, Kioumourtzoglou MA, Roberts AL, O'Reilly ÉJ, Ascherio A, Weisskopf MG. Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. Am J Epidemiol. 2019;188(4):768-775. doi:10.1093/aje/kwy288.

[203] Gustavson K, Ask H, Ystrom E, Stoltenberg C, Lipkin WI, Surén P, Håberg SE, Magnus P, Knudsen GP, Eilertsen E, Bresnahan M, Aase H, Mjaaland S, Susser ES, Hornig M, Reichborn-Kjennerud T. Maternal fever during pregnancy and offspring attention deficit hyperactivity disorder. Sci Rep. 2019 Jul 2;9(1):9519. doi: 10.1038/s41598-019-45920-7. PMID: 31266998; PMCID: PMC6606630.

5.14). Similar associations were reported regardless of whether or not the mother took acetaminophen (with acetaminophen OR = 1.35, 95% CI 0.96–1.90; without acetaminophen OR = 1.32, 95% CI 1.01–1.71). While I weigh this study only slightly in my consideration of the evidence, it supports the role of maternal fever as a risk for offspring ADHD and provide evidence that maternal acetaminophen use does not increase the risk of ADHD in offspring.

b. **Results Of Case Control Study**

Chen 2019.[204] This is the only retrospective case-control study that involved study subjects with a clinical diagnosis of ADHD. Researchers conducted a retrospective case-control study using a matched mother-child pair sample identified from the Taiwan Longitudinal Health Insurance Database to investigate the relationship between prenatal exposure to acetaminophen and the offspring's ADHD risk. Exposure was determined by review of the health insurance database, and demographic characteristics were collected together with clinical visit dates, disease diagnoses, and prescriptions. The outcome of ADHD was based on a diagnosis made by a psychiatrist. Logistic regression analysis with adjustment for demographic data, gestational infections, comorbid perinatal conditions, and maternal mental health disorders showed that exposure to acetaminophen in the second trimester (OR = 1.19, 95% CI 1.00, 1.40) or in both first and second trimesters (OR = 1.28; 95% CI 1.00, 1.64) or in any trimester (OR = 1.20, 95% CI 1.01, 1.42) was associated with increased risk of ADHD, though the bottom range of the confidence interval included or was barely above 1.0 in each instance. Cumulative doses of acetaminophen calculated by regression analysis were not related to increased ADHD risk (2nd trimester OR = 1.13, 95% CI 0.76, 1.69; both 1st and 2nd trimesters OR = 0.98, 95% CI 0.50, 1.91), which led the authors to conclude that this study showed no "dose-dependent relationship between prenatal acetaminophen use and the offspring's ADHD risk." Finally, exposure to acetaminophen in utero was likely under-reported given that this information was derived from an insurance database, which would not have accounted for all such exposures, because acetaminophen is an over the counter medication.

[204] Chen MH, Pan TL, Wang PW, et al. Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan. J Clin Psychiatry. Published online 2019:7.

2. Epidemiological Studies Assessing Neurobehavioral Outcomes Other Than Clinical ADHD Diagnosis

As discussed earlier in this report (*see* Section VI.C.3, above), specificity of outcome is a hallmark of a well-designed epidemiologic study. In the absence of specificity, associations have less reliability and validity. In part for this reason, studies that do not use a clinical diagnosis of ADHD as an endpoint are insufficient to establish a causal inference. For example, the SDQ screening tool, which was used in seven different cohort studies, has a positive predictive value for diagnosis of ADHD that has been reported to be as low as 12 percent.[205]

Nonetheless, because plaintiffs' experts rely heavily on a number of these studies, I address them in Appendix 2, below.

Notably, while plaintiffs' experts repeatedly claim that it is important to consider studies assessing all neurodevelopmental disorders, not just the studies with clinical diagnoses of ADHD, Dr. Baccarelli has stated otherwise in his published work. In Laue et al. 2019 (of which Dr. Baccarelli was a co-author), the authors addressed a number of studies that used screening tools as opposed to clinical diagnoses to measure outcomes[206] and stated that "the lack of an objective, clinical measurement of neurodevelopment in these studies may have caused

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[205] 222. Russell G, Rodgers LR, Ford T. The strengths and difficulties questionnaire as a predictor of parent-reported diagnosis of autism spectrum disorder and attention deficit hyperactivity disorder. PLoS One. 2013 Dec 3;8(12):e80247. doi: 10.1371/journal.pone.0080247. PMID: 24312466; PMCID: PMC3848967.

[206] Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016;45(6):dyw115. doi:10.1093/ije/dyw115.

Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. Int J Epidemiol. 2016;45(6):dyw296. doi:10.1093/ije/dyw296.

Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016;170(10):964. doi:10.1001/jamapediatrics.2016.177.

Thompson JMD, Waldie KE, Wall CR, Murphy R, Mitchell EA, the ABC study group. Associations between Acetaminophen Use during Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years. Hashimoto K, ed. PLoS ONE. 2014;9(9):e108210. doi:10.1371/journal.pone.0108210.

Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MMHJ, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero : a propensity score matched cohort study. Int J Epidemiol. 2016;45(6):dyw192. doi:10.1093/ije/dyw192.

overestimation of the adverse effects of acetaminophen—parents of children with some symptoms may overreport those traits—leading to unnecessary concern about the safety of acetaminophen."[207] The same paper also dismisses Tronnes et al. 2020, a study that concluded acetaminophen does not have a negative impact on child communication, behavior, or temperament. Specifically, Dr. Baccarelli found this study to be not "persuasive" because it "did not have ADHD as an endpoint and was forced to rely on less clearly defined child outcomes."[208]

Of note, the "less clearly defined child outcomes" used by Tronnes et al. 2020 included the Ages and Stages Questionnaire, which is the same screening tool used in Brandlistuen et al. 2013. Yet, when discussing Brandlistuen et al. 2013 (a study that reported an association between maternal acetaminophen use and adverse neurodevelopmental outcomes), plaintiffs' experts collectively failed to make this criticism. Dr. Louie also described Brandlistuen et al. 2013 as having "employed the strongest study design."[209]

The specificity concerns are increased by the fact that many of the studies apply screening tools for ADHD incorrectly. This type of misuse occurred repeatedly in studies using the CBCL, SDQ, and ASQ screening tools. The CBCL was designed to be completed by multiple informants (e.g., parent and teacher) and to be administered on multiple occasions to look for persistence of symptoms.[210] Thomas Achenbach, the author of the Child Behavior Checklist, was adamant that comparative data from multiple informants are essential for accurate assessment of child psychopathology.[211] Yet, only one of the *five* studies that used the CBCL as an outcome

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[207] Laue HE, Cassoulet R, Abdelouahab N, et al. Association Between Meconium Acetaminophen and Childhood Neurocognitive Development in GESTE, a Canadian Cohort Study. Toxicol Sci. 2019;167(1):138-144. doi:10.1093/toxsci/kfy222.

[208] Baccarelli Rep. at 116.

[209] Louie Rep. ¶ 71.

[210] Achenbach TM. Manual for the Child Behavior Checklist/4-18 and the 1991 Profile. Burlington, VT: University of Vermont, Department of Psychiatry, 1991.

[211] Achenbach, T. M. (2006). As others see us: Clinical and research implications of cross-informant correlations for psychopathology. Current Directions in Psychological Science, 15, 94–98.

measurement actually had the test completed by multiple informants,[212] and none reported results from multiple occasions.

Other screening instruments such as BRIEF, ODD symptom score, SDQ and ASQ were also designed for data collection from multiple informants. Of the 12 studies[213] using such

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[212] Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MMHJ, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero : a propensity score matched cohort study. Int J Epidemiol. 2016;45(6):dyw192. doi:10.1093/ije/dyw192 (parent-report).

Parker SE, Collett BR, Werler MM. Maternal acetaminophen use during pregnancy and childhood behavioural problems: Discrepancies between mother- and teacher-reported outcomes. Paediatr Perinat Epidemiol. 2020;34(3):299-308. doi:10.1111/ppe.12601.

Tovo-Rodrigues L, Carpena MX, Martins-Silva T, Santos IS, Anselmi L, Barros AJD, Barros FC, Bertoldi AD, Matijasevich A. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. Paediatr Perinat Epidemiol. 2020 May;34(3):278-286. doi: 10.1111/ppe.12649. Epub 2020 Mar 20. PMID: 32196712.

Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. Paediatr Perinat Epidemiol. 2020;34(3):247-256. doi:10.1111/ppe.12568.

Sznajder KK, Teti DM, Kjerulff KH. Maternal use of acetaminophen during pregnancy and neurobehavioral problems in offspring at 3 years: A prospective cohort study. Sun K, ed. PLOS ONE. 2022;17(9):e0272593. doi:10.1371/journal.pone.0272593.

[213] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

Thompson JMD, Waldie KE, Wall CR, Murphy R, Mitchell EA, the ABC study group. Associations between Acetaminophen Use during Pregnancy and ADHD Symptoms Measured at Ages 7 and 11 Years. Hashimoto K, ed. PLoS ONE. 2014;9(9):e108210. doi:10.1371/journal.pone.0108210.

Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. Int J Epidemiol. 2016;45(6):dyw296. doi:10.1093/ije/dyw29.

Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MMHJ, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero : a propensity score matched cohort study. Int J Epidemiol. 2016;45(6):dyw192. doi:10.1093/ije/dyw192.

Skovlund E, Handal M, Selmer R, Brandlistuen RE, Skurtveit S. Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids. Pharmacoepidemiol Drug Saf. 2017;26(6):625-634. doi:10.1002/pds.4170.

Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016;170(10):964. doi:10.1001/jamapediatrics.2016.177.

Ruisch IH, Buitelaar JK, Glennon JC, Hoekstra PJ, Dietrich A. Pregnancy risk factors in relation to oppositional-defiant and conduct disorder symptoms in the Avon Longitudinal Study of Parents and Children. J Psychiatr Res. 2018;101:63-71. doi:10.1016/j.jpsychires.2018.02.020.

instruments, six (Thompson et al. 2014; Liew et al. 2016b, Ruisch et al. 2018, Golding et al. 2019; Rifas-Shiman et al. 2020; Inoue et al. 2021) reported results for more than one informant. As depicted in the table below, five of those six studies reported different results from different informants—with many results (set forth in red and bold) showing no statistically significant association—substantially undermining the validity of any association ultimately observed:

Study	Parent Report	Teacher or Child Report
Thompson et al. 2014	**SDQ at 11 years:** **β=0.8 (0.0, 1.6)**	SDQ at 11 years: β=1.1 (0.2, 2.0)
Liew et al. 2016b[214]	**Executive function (BRIEF):** **General Executive Composite** **OR = 1.3 (0.8, 2.1)** **Behavioural Regulation Index** **OR = 1.3 (0.8, 2.1)** **Metacognition Index** **OR = 1.5 (0.9, 2.3)**	**Executive function (BRIEF):** **General Executive Composite** **OR = 1.2 (0.7, 2.0)** **Behavioural Regulation Index** **OR = 1.0 (0.6, 1.6)** **Metacognition Index** **OR = 1.3 (0.8, 2.2)**
Ruisch et al. 2018	**ODD symptom score:** **IRR 1.01 (0.89, 1.15)**	ODD symptom score: OR=1.24 (1.05, 1.47)
Golding et al. 2019[215]	SDQ hyperactivity scores: 2 of 7 measures had associations	**SDQ hyperactivity scores:** **No statistically significant associations**

Golding J, Gregory S, Clark R, Ellis G, Iles-Caven Y, Northstone K. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. Paediatr Perinat Epidemiol. 2020;34(3):257-266. doi:10.1111/ppe.12582.

Tovo-Rodrigues L, Schneider BC, Martins-Silva T, et al. Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. BMC Psychiatry. 2018;18(1):368. doi:10.1186/s12888-018-1942-1.

Rifas-Shiman SL, Cardenas A, Hivert M, Tiemeier H, Bertoldi AD, Oken E. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. Paediatr Perinat Epidemiol. 2020;34(3):287-298. doi:10.1111/ppe.12596.

Inoue K, Ritz B, Ernst A, et al. Behavioral Problems at Age 11 Years After Prenatal and Postnatal Exposure to Acetaminophen: Parent-Reported and Self-Reported Outcomes. Am J Epidemiol. 2021;190(6):1009-1020. doi:10.1093/aje/kwaa257.

[215] Authors indicate that DAWBA was performed by both teacher and parent. However, the publication and supplemental tables do not present these results separate by informant (teacher or parent). Therefore, I am unable to include those results in this table.

Study	Parent Report	Teacher or Child Report
Rifas-Shiman et al. 2019	BRIEF Global Executive Composite: β=0.76 (0.32, 1.20) Behavior Regulation Index β=0.61 (0.18, 1.20) BRIEF Metacognition Index β=0.62 (0.20, 1.04) SDQ total difficulties β=0.24 (0.02, 0.46) **Prosocial** **β=0.06 (-0.02, 0.14)**	BRIEF Global Executive Composite: β=0.62 (0.06, 1.18) Behavior Regulation Index β=0.62 (0.06, 1.18) **BRIEF Metacognition Index** **β=0.55 (-0.02, 1.12)** SDQ total difficulties β=0.35 (0.05, 0.65) **Prosocial** **β=0.04 (-0.16, 0.08)**
Inoue 2021	SDQ at 11 years: **Internalizing** **aRR = 1.09 (1.00, 1.19)** **Externalizing** **aRR = 1.07 (0.99, 1.15)** Emotional symptoms aRR = 1.16 (1.09, 1.24) **Conduct Problems** **aRR = 1.05 (0.94, 1.17)** Hyperactivity aRR = 1.12 (1.02, 1.24) **Peer Problems** **aRR = 0.99 (0.90, 1.08)** **Prosocial behavior** **aRR = 0.92 (0.85, 1.00)**	SDQ at 11 years: Internalizing aRR = 1.13 (1.04, 1.23) Externalizing aRR = 1.13 (1.05, 1.22) Emotional symptoms aRR = 1.17 (1.02, 1.34) Conduct Problems aRR = 1.15 (1.01, 1.32) Hyperactivity aRR = 1.18 (1.08, 1.29) **Peer Problems** **aRR = 1.09 (0.94, 1.26)** **Prosocial behavior** **aRR = 1.05 (0.94, 1.17)**

Additionally, the SDQ and ASQ are designed to have information at multiple time points. Only two studies reported data for more than one time point (Thompson et al. 2014; Tovo-Rodrigues et al. 2018), and both showed that reported results were transitory (i.e., not consistent over time). Thus, not only are these studies of little, if any, value in determining causation because they do not involve a diagnosis of ADHD, but their results are also unreliable for additional reasons.

Plaintiffs also rely on studies utilizing tools to assess language delay and IQ, but these measures are not diagnostic of ADHD. Notably, Dr. Baccarelli has explicitly stated that

intelligence score "does not directly bear on ADHD or ASD" and that "behavior and intelligence are different neuropsychological constructs."[216]

3. The Meta-Analyses Are Not Tied To ADHD Diagnosis

As detailed in Appendix 2, below, several meta-analyses purport to analyze ADHD in the context of a child's exposure to acetaminophen through maternal use by pooling data from underlying studies, but all of these meta-analyses include underlying studies that did not limit the outcome being investigated to an ADHD diagnosis. Only one, Ricci et al. 2023, performed a subgroup analysis that was limited to studies involving diagnosed ADHD. For this reason and a number of others, the meta-analyses do not support plaintiffs' causal hypothesis.

All of the meta-analyses claiming to show an association between in utero acetaminophen exposure and ADHD, or purported ADHD-related symptoms or behaviors, are subject to significant limitations that make it impossible to draw conclusions regarding causation based on them.

For example, ***Gou et al. 2019***[217] included eight cohort studies with a total of 244,940 participants and reported a pooled adjusted risk ratio of 1.25 (95% CI 1.17, 1.34), but only three of the eight studies investigated an ADHD diagnosis. The authors note that the summary measures of association suffer from the same potential for residual confounding as the studies on which they are based and caution against concluding that this association is causal, "because potentially unidentified or inadequately controlled confounding factors in the included studies may have unpredictable effects on the observed association."

Masarwa et al. 2020[218] is an update to the author's prior meta-analysis from 2018 (which also addressed ASD, as discussed above). Neither meta-analysis is limited to studies that used a clinical diagnosis of ADHD as an outcome measurement (only two of the seven cohorts investigated ADHD diagnosis). The authors report pooled adjusted estimates for ADHD that are weak but statistically significant (aRR= 1.35; 95% CI 1.25, 1.46). However, the authors also

[216] Baccarelli Rep. at 108.

[217] Gou X, Wang Y, Tang Y, et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. Aust N Z J Psychiatry. 2019;53(3):195-206. doi:10.1177/0004867418823276.

[218] Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? Paediatr Perinat Epidemiol. 2020;34(3):309-317. doi:10.1111/ppe.12615.

reported that a sensitivity analysis for unmeasured confounding showed that a confounder of 1.69 on the RR scale would reduce the proportion of studies with a true effect size of RR >1.10 to 10%.

In addition, the authors conducted a bias analysis, which found that after correction for bias, no single study included in the analysis showed a statistically significant association, and the overall meta-analysis did not show a significant association. Indeed, the authors ultimately concluded that bias analysis suggests that the previously reported association between acetaminophen use during pregnancy and an increased risk of ADHD in offspring is likely due to unmeasured confounding.

Alemany et al. 2021[219] (which also addressed ASD) conducted a meta-analysis in which ADHD symptoms were assessed at 4-12 years of age using validated instruments, with hospital diagnoses of ADHD only available in one cohort. Across cohorts, there was substantial variation in the proportion of children presenting borderline/clinical symptoms, with 1.2%–12.2% presenting ADHD symptoms. The failure to use ADHD diagnosis as the relevant outcome, coupled with the admitted heterogeneity of the outcomes that were measured, makes it impossible to know whether there is any clinical significance to the reported association between maternal acetaminophen use and ADHD symptoms (OR = 1.21; 1.07–1.36).

Ricci et al. 2023[220] (which likewise addressed ASD and is discussed above) sought to perform an analysis of various neurobehavioral outcomes, but determined that only ADHD had a sufficient number of comparable studies to conduct a meta-analysis. The authors report that prenatal acetaminophen exposure was associated with elevated risk of ADHD (pooled RR=1.32; 95% CI 1.20, 1.44), with moderate heterogeneity across studies. The paper also includes one analysis limited to studies that involve an ADHD diagnosis and reports a slightly higher risk (pooled RR=1.47; 95% CI 1.12, 1.92).

Notably, the authors acknowledge several limitations in the underlying data used in the meta-analysis including the fact that exposures and outcomes were self-reported by caregivers, introducing bias, and that there was incomplete control for confounding by indication. The authors also note the variability across studies in terms of what indications were measured and point out

[219] Alemany S. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. Eur J Epidemiol. 2021;36:12. doi:https://doi.org/10.1007/s10654-021- 00754-4.

[220] Ricci C, Albanese C, Pablo L In utero acetaminophen exposure and child neurodevelopmental outcomes: Systematic review and meta-analysis Paediatr Perinat Epidemiol. 2023;00:1–12.

that very few studies measured parental ADHD, which may result in residual confounding by familial/genetic factors.

C. The Bradford Hill Considerations Do Not Support A Causal Link

As detailed in Section VI.C. above, a Bradford Hill analysis is only called for where the epidemiologic literature establishes an association that is "perfectly clear-cut." In my opinion, the literature has not identified an association between maternal acetaminophen use during pregnancy and ADHD in offspring that is "perfectly clear-cut and beyond what we would care to attribute to the play of chance" for the many reasons set forth in the preceding sub-sections. As such, I do not believe a Bradford Hill analysis is even warranted.[221]

Nonetheless, as with ASD, application of the Bradford Hill criteria confirms that the literature does not support a causal inference between acetaminophen use during pregnancy and ADHD in offspring.

1. The Strength Of Association Factor Is Not Met

The association between maternal use of acetaminophen and ADHD in children, when observed, is almost always far less than that—and indeed does not even reflect a doubling of the risk—rendering it weak by definition. This weak association is of particular concern for reasons similar to those with respect to ASD—i.e., low associations can easily be explained by bias and/or confounding, both of which are concerns in the APAP literature.

a. The Epidemiological Studies Are Biased

First, as with ASD, bias is a significant concern when analyzing the weak and imprecise associations reported by the studies assessing maternal acetaminophen exposure and ADHD diagnosis in offspring. One particular bias common in these studies is exposure misclassification bias.[222] The strong genetic etiology of ADHD makes it more likely mothers with an affected child

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[221] Hill A B (1965). The environment and disease: association or causation? Proceedings of the Royal Society of Medicine, 58(5), 295–300.

[222] Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

Gustavson K, Ystrom E, Ask H, et al. Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder – a longitudinal sibling control study. JCPP Adv. 2021;1(2). doi:10.1002/jcv2.12020.

Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal Exposure to Acetaminophen and

are themselves affected by the symptoms of these disorders, including anxiety neuroticism, and impulsivity, compared to mothers of neurotypical children. This would lead to differential reporting of acetaminophen use, as anxiety is known to lead to both increased retention in longitudinal studies[223] and results in greater recall and reporting of past events.[224]

Dr. Baccarelli asserts in his report that there is no reason to suspect that misclassification would be related to exposure and that any bias would therefore be toward the null.[225] But, while Dr. Baccarelli cites the Masarwa 2020 meta-analysis for this proposition, the Masarwa 2020 authors actually explain that "a healthy mother who experienced an uneventful pregnancy will be less likely to report medication use during and after pregnancy than a mother with co-morbidities and an eventful pregnancy. This misclassification will likely result in over-reporting of acetaminophen use."[226] As a result, the authors state that the sensitivity analysis (which Dr. Baccarelli references in his report) "may not be representative of the true effect of exposure misclassification bias."

Another potential concern in several of the studies relates to the loss to follow-up.[227] Bias can be introduced if the individuals who drop out of a cohort study differ with respect to the exposure and/or outcome from those who remain in the study. Research on retention and attrition

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Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

Liew Z, Kioumourtzoglou MA, Roberts AL, O'Reilly ÉJ, Ascherio A, Weisskopf MG. Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. Am J Epidemiol. 2019;188(4):768-775. doi:10.1093/aje/kwy288.

[223] Dupuis M, Strippoli MP, Gholam-Rezaee M et al Mental disorders, attrition at follow-up, and questionnaire non-completion in epidemiologic research Int J Methods Psychiatr Res. 2019;28:e1805.

de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol. 2000 Dec 1;152(11):1039-47. doi: 10.1093/aje/152.11.1039. PMID: 11117613.

[224] Bekkhus M, Lee Y, Nordhagen R, Magnus P, Samuelsen SO, Borge AIH. Re-examining the link between prenatal maternal anxiety and child emotional difficulties, using a sibling design. Int J Epidemiol. 2018 Feb 1;47(1):156-165. doi: 10.1093/ije/dyx186. PMID: 29024982; PMCID: PMC5837524.

[225] Baccarelli Rep. at 62, 93.

[226] Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? Paediatr Perinat Epidemiol. 2020;34(3):309-317. doi:10.1111/ppe.12615.

[227] Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

in longitudinal studies has shown that individuals with anxiety are less like to drop out of studies.[228] If the individuals who are retained by the study have higher rates of anxiety or depression, which is also associated with offspring ADHD, the bias will lead to overestimation of risk.[229]

This problem was identified in Rifas-Shiman et al. 2020, in which the investigators "observed some differences in baseline covariates between participants and those lost to follow-up."[230] The cohort from which Liew et al. 2014, discussed above, obtained data had a follow-up loss of approximately 40%. Further, in Baker et al. 2021, only 14.2% of the children who had meconium collected agreed to return to have an MRI performed. As a result, there is significant risk that bias was introduced in these studies due to the characteristics of the population of participants who continued with the study versus those who did not follow up.

Dr. Baccarelli speculates that the Danish National Birth Cohort loss to follow-up included women with the highest likelihood of both having an affected child and also taking acetaminophen, but he cites no data to support his position.[231] Dr. Baccarelli also states that, because of the prospective nature of cohort studies, they are not typically susceptible to sources of bias and that he therefore rated nearly all cohort studies at "low risk of bias."[232] To be sure, prospective designs reduce some forms of bias (especially, recall bias), but all observational studies have limitations, and issues such as loss to follow-up and misclassification bias are concerns that must be evaluated.

b. The Studies Are Affected By Confounding

Confounding is also particularly concerning when assessing the risk of exposure to maternal acetaminophen use and ADHD in offspring because there is still much that is unknown about the causes of ADHD. Dr. Baccarelli's statement that "any theoretical confounder associated with consumer APAP would have to have enormous power in order to explain the association" is

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[228] Dupuis M, Strippoli MP, Gholam-Rezaee M et al Mental disorders, attrition at follow-up, and questionnaire non-completion in epidemiologic research Int J Methods Psychiatr Res. 2019;28:e1805.

de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol. 2000 Dec 1;152(11):1039-47. doi: 10.1093/aje/152.11.1039. PMID: 11117613.

[229] Dupuis M, Strippoli MP, Gholam-Rezaee M et al Mental disorders, attrition at follow-up, and questionnaire non-completion in epidemiologic research Int J Methods Psychiatr Res. 2019;28:e1805.

[230] Rifas-Shiman SL, Cardenas A, Hivert M, Tiemeier H, Bertoldi AD, Oken E. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. Paediatr Perinat Epidemiol. 2020;34(3):287-298. doi:10.1111/ppe.12596.

[231] Baccarelli Rep. at 82.

[232] Baccarelli Rep. at 139.

wrong.[233] In fact, a single confounder of only modest strength can significantly attenuate an association. As discussed above, Masarwa et al. 2020 reported that a confounder of just RR 1.69 would reduce to 10% the proportion of studies with a true effect size of RR > 1.10. And Dr. Baccarelli does not address the fact that multiple confounders can influence the same association. It is well-accepted that most outcomes are a function of multiple factors, and any analysis of a particular exposure and outcome must therefore account for those multiple factors. As discussed throughout this report, there are several potential confounders at issue here, including most importantly, genetics and confounding by indication.

(1) Sibling-control analysis attenuated any noted association with ADHD

First, as discussed above, Gustavson et al. 2021 illustrates the necessity of adjusting for genetics because using a sibling-control analysis there attenuated any potential association between maternal acetaminophen use while pregnant and an ADHD diagnosis in offspring.

Several additional recent studies used sibling control analyses when assessing risk factors for ADHD and support the same conclusion. The following table illustrates these findings (including the Gustavson et al. 2021 finding referenced above):

Study	Risk Factor	Risk Without Sibling Control	Risk with Sibling Control
Chen 2014	Maternal Obesity	aHR=1.64, 95% CI 1.57, 1.73	aHR=1.15, 95% CI 0.85, 1.56
Skoglund 2014	Maternal smoking (≥10 cig/day)	aRR=2.04, 95% CI 1.95, 2.13	aRR=0.84, 95% CI 0.65, 1.06
Curran 2016	Elective-c-section	aHR=1.16, 95% CI 1.04, 1.29	aHR=1.05, 95% CI 0.93, 1.18
Wiggs 2017	Oxytocin-induced labor induction	aHR=1.23, 95% CI 1.19, 1.28	aHR=0.99, 95% CI 0.91, 1.07
Axelsson 2019	C-section: intrapartum (IP) and prelabor (PL)	aHR_{IP}=1.10, 95% CI 1.04, 1.16 aHR_{PL}=1.11, 95% CI 1.05, 1.17	aHR_{IP}=1.09, 95% CI 0.97, 1.24 aHR_{PL}=1.03, 95% CI 0.91, 1.16
Gustavson 2021	Maternal Acetaminophen (≥ 29 days)	aHR = 2.02, 95% CI, 1.17, 3.25	aHR = 1.06, 95% CI 0.51, 2.05
Hegvik 2023	Labor epidural analgesia (pooled)	aHR=1.20, 95% CI=1.19-1.21	aHR=0.99, 95% CI=0.96-1.02

[233] Baccarelli Rep. at 170.

Other than Gustavson et al. 2021, no other study that assessed maternal acetaminophen use and an ADHD diagnosis in offspring utilized the sibling control methodology to address the underlying genetic risk.[234] Moreover, two of the studies with the largest reported associations (Ji et al. 2018, Baker et al. 2020) do not attempt to adjust for genetics at all. This omission is a significant limitation in the literature.

In his report, plaintiffs' expert Dr. Louie discusses the benefits of the sibling control methodology and states that he gave "the greatest weight" to a study that used the sibling control analysis "because it employed the strongest study design."[235] Similarly, when discussing risk factors for ASD, Dr. Hollander explained that a 2016 study reported an increased risk of ASD in children with overweight and obese mothers, but noted that this risk factor "still needs to be studied, [because] in another large study, the sibling analysis did not reveal any association between elevated BMI and ASD risk, even though there was a relationship at the population level."[236]

Nevertheless, Dr. Baccarelli is critical of Gustavson et al. 2021 because the authors acknowledged that potential mediating factors may lead to under-estimation of association estimates.[237] Dr. Baccarelli hypothesizes that there are some intervening variables through which acetaminophen use increases the risk of ADHD among siblings, such that controlling for sibling status erroneously hides a true causal relationship between acetaminophen use and ADHD.

This argument has several problems. First, it fails to acknowledge that sibling control is widely used by the epidemiology community and, more specifically, has been used by various groups when assessing potential causes of ADHD, as noted above. The possibility of mediation is present in any sibling-control design; yet, the scientific community has accepted sibling control as a means for attempting to isolate genetic confounding in epidemiologic research.

Moreover, the study cited in Gustavson et al. 2021—Sjolander and Zetterqvist 2017 (which is also the sole support for Dr. Baccarelli's statement about mediation)—does not suggest that

[234] Leppert B, Havdahl A, Riglin L, et al. Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures. JAMA Psychiatry. 2019;76(8):834. doi:10.1001/jamapsychiatry.2019.0774.

[235] Louie Rep. at 25.

[236] Hollander Rep. at 25 (citing Gardner et al. 2015).

[237] Baccarelli Rep. at 117.

mediation is more likely than not to bias outcomes toward the null in every sibling-control study. Rather, it states that "[c]ontrolling for mediators may or may not lead to bias, depending on the research question."[238] This is a very general statement that simply calls for a study-specific analysis. Gustavson et al. 2021 correctly acknowledge it as a conceptual limitation, but do not suggest there is a reason to believe that it actually applies to their findings.

Dr. Baccarelli does not provide any basis to support his suggestion that the various alleged biological mechanisms (e.g., oxidative stress) are mediators. To determine whether a variable is a mediator, a mediation analysis must be conducted. However, this analysis requires the inclusion of data on the potential mediator. No epidemiologic data exists on the various biological mechanisms that Dr. Baccarelli mentions. Thus, a mediation analysis cannot be performed to determine their relevance. It is insufficient to merely pose a hypothesis that a mediator such as oxidative stress discounts the attenuation in the sibling control analysis presented by Gustavson et al. 2021.

(2) Associations with ADHD and pre-natal, post-natal, and paternal use of acetaminophen demonstrate residual confounding and confounding by indication

Dr. Baccarelli's related argument that other studies have ruled out a genetic explanation without sibling controls through the use of a "negative control" is flawed.[239] Dr. Baccarelli cites four studies that used a negative control: Stergiakouli et al. 2016, Ystrom et al. 2017, Tronnes et al. 2020 and Liew et al. 2019. In fact, these studies provide evidence of residual confounding.

As to Stergiakouli et al. 2016, a complete analysis of the study's reported results indicate that residual confounding is present because the statistically significant adjusted associations are stronger for postnatal paternal use than maternal use during pregnancy (as shown in the table below). In other words, both paternal use of acetaminophen was more strongly associated with ADHD than prenatal use—which is the opposite of what would be expected if in utero exposure to acetaminophen were the cause of ADHD:

[238] Sjölander A, Zetterqvist J. Confounders, Mediators, or Colliders: What Types of Shared Covariates Does a Sibling Comparison Design Control For? Epidemiol Camb Mass. 2017;28(4):540-547. doi:10.1097/EDE.0000000000000649.

[239] E.g., Baccarelli Rep. at 73.

SDQ Domain	Maternal Use at 18 Weeks of Pregnancy	Maternal Use at 32 Weeks of Pregnancy	Postnatal Paternal Use
Conduct problems	aHR = 1.14 (CI 95% 0.96, 1.35)	aHR = 1.36 (CI 95% 1.14-1.63)	aHR = 1.63 (CI 95% 1.11-2.40)
Hyperactivity problems	aHR = 1.17 (CI 95% 1.00, 1.38)	aHR = 1.26 (CI 95% 1.07-1.49)	aHR = 1.41 (CI 95% 1.02-1.97)

Of note, the investigators received strong criticisms for failing to discuss the adjusted associations in the actual article. In response, the investigators stated that, "[r]egarding clinical significance, we do not claim that our findings are clinically significant or suggest that there should be a change in public health advice following our study, which is explicitly stated in the abstract and discussion."[240]

Evidence of residual confounding was also present in Ystrom et al. 2017. As delineated in the table below, extracted from the study, a purported dose-response relationship was present for paternal acetaminophen use six months before pregnancy, suggesting confounding by genetic/familial factors.

TABLE 3 HRs for Offspring ADHD by Number of Days of Paternal Acetaminophen Use 6 Months Before Pregnancy

	No. of Fathers Reporting Each Category	HR[a]	95% CI
No use	64 348	1.00	Reference
1–7 d	8887	1.10	(0.92–1.30)
8–28 d	1079	1.81	(1.26–2.60)
29 or more d	657	2.06	(1.36–3.13)

[a] Adjusted for year of birth, paternal age, and parity.

As to Tronnes et al. 2020, I agree with Dr. Bacarrelli that the study has methodological limitations. The study reports a small increase in communication problems (aRR = 1.19, 95% CI 1.02, 1.38) for maternal use before pregnancy. However, for the reasons previously stated, pre-pregnancy use is not a valid negative control.

[240] Stergiakouli E, Thapar A, Davey Smith G. Acetaminophen in Pregnancy and Adverse Childhood Neurodevelopment-Reply. JAMA Pediatr. 2017 Apr 1;171(4):396-397. doi:10.1001/jamapediatrics.2016.5040. PMID: 28192550.

With respect to Liew et al. 2019, the assertion that maternal use of acetaminophen before and after pregnancy is a negative control for genetics/familial factors is flawed. Dr. Baccarelli states that pre- and post-pregnancy use is an adequate negative control because the underlying factors, such as genetics, chronic illness, family and social factors, and/or general medication use behaviors are the same for women before, after, and during pregnancy (a time-invariant variable).[241] Therefore, if these factors are causing the associations, a statistically significant association for maternal acetaminophen use would be present both before, during, and after pregnancy. But that is not true for several reasons, as discussed throughout this report.

Chen et al. 2019 also purported to perform a negative control analysis based on maternal pre-pregnancy use, reporting an association between prenatal acetaminophen exposure and ADHD diagnosis (aOR = 1.20, 95% CI 1.01, 1.42), but no statistically significant association for use during the three months before pregnancy (aOR = 1.06, 95% CI 0.90, 1.25). For the reasons I previously described, this negative control is not valid. Accordingly, the use of sibling controls provide strong evidence of genetic/familial confounding in the studies assessing the association with maternal use of acetaminophen and the development of ADHD, and that evidence has not been refuted by studies using other negative controls.

Second, confounding by indication must also be accounted for in assessing whether the weak association reported in some studies between prenatal acetaminophen use and the development of ADHD is causal.

The ADHD studies attempted to adjust for confounding by indication to varying degrees, if at all.

- Baker et al. 2020 did nothing to adjust for indication of use, making its results highly susceptible to residual confounding.
- Ji et al. 2018 and 2020 only adjust for fevers recorded in medical records. However, such a narrow adjustment ignores pain, migraines, fevers not reported to a medical provider, and any information relating to co-morbidities that could have caused or could have been related to the indication of acetaminophen use.
- Liew et al. 2019 adjusted for reported pain and fever medications, but that is similarly insufficient due to the study's reliance on maternal report.

[241] Baccarelli Rep. at 73.

- Liew et al. 2014 adjusted for the presence of diseases or conditions that may trigger use of acetaminophen, such as muscle and joint diseases, fever, and inflammation or infections. Such an adjustment cannot evaluate whether acetaminophen was actually taken for any of these issues.
- Ystrom et al. 2017 is the only study with an outcome measurement of ADHD diagnosis that had actual data on indication of use. However, the supplemental table included in that study reveals that approximately 32% of mothers who used acetaminophen did not recall what they used it for. As previously discussed, there is an interplay between underlying maternal characteristics and recall that could differentially bias these results. Therefore, an analysis using such incomplete data limits the clinical relevance of these results.

In short, the strength consideration is not satisfied, and there are several likely confounders and biases to explain the weak association that was found in some studies.

2. The Epidemiologic Studies Are Inconsistent

As previously discussed, consistency asks whether the same association exists in different study designs and different study populations. The body of literature assessing a potential association between maternal acetaminophen use and ADHD in offspring is highly inconsistent.

For example, two cohort studies (Liew 2014 and Ystrom 2017) analyzed rates of ADHD/HKD diagnosis according to maternal acetaminophen use by trimester. A comparison of the adjusted results demonstrates that the results are inconsistent (with statistically insignificant results in bold red):

Trimester(s) Analyzed	Liew 2014 aHR for HKD	Ystrom 2017 aHR for ADHD
Any 1 trimester	Not Performed	1.07 (95% CI 0.96, 1.19)
1st trimester only	1.35 (95% CI 1.07, 1.72)	**1.12 (95% CI 0.94, 1.32)**
2nd trimester only	**1.26 (95% CI 0.91, 1.73)**	**1.04 (95% CI 0.92, 1.18)**
3rd trimester only	**1.22 (95% CI 0.97, 1.53)**	**1.12 (95% CI 0.75, 1.67)**
Any 2 trimesters	Not Performed	1.22 (95% CI 1.07, 1.38)
1st and 2nd trimesters	**1.31 (95% CI 0.93, 1.95)**	1.21 (95% CI 1.06, 1.39)
2nd and 3rd trimesters	**1.30 (95% CI 0.92, 1.84)**	**1.20 (95% CI 0.87, 1.66)**
1st and 3rd trimesters	1.41 (95% CI 1.08, 1.84)	**1.34 (95% CI 0.77, 2.34)**
All 3 trimesters	1.61 (95% CI 1.30, 2.01)	**1.27 (95% CI 0.99, 1.62)**

Further, assuming the exposure data in Ji et al. 2018 and Ji et al. 2020, which comes from cord blood and maternal plasma after delivery, is considered to be third-trimester usage (which is questionable because the maternal use of acetaminophen occurred, at most, a few hours before

delivery for the acetaminophen to have been detectable due to the half-life of acetaminophen), the results reported in Ji et al. 2018 and Ji et al. 2020 (which were statistically significant) are inconsistent with the data reported above in Liew et al. 2014 and Ystrom et al. 2017.

There are also inconsistencies across the studies (discussed in more detail in Appendix 2) that use screening tools to evaluate whether maternal acetaminophen use increases the risk of developing ADHD in offspring. The two screening tools used most frequently to collect data were the CBCL (used by five studies) and the Strength and Difficulties Questionnaire (SDQ) (used by seven studies).

As summarized in the table below, two of the five studies using the CBCL reported no outcome associations with acetaminophen usage, and the other three studies reported no association for the majority of the problems assessed:

Child Behavior Check List (CBCL)

Study	Results
Vlenterie 2016	No associations were present for short term use. No association were present for nine of 10 CBCL items assessed for greater than 28 days of acetaminophen exposure.
Parker et al. 2020	No associations were reported when adjusted for indication/illness.
Tovo-Rodrigues et al. 2020	No associations were reported for 8 CBCL items assessed and no associations were reported for two measures aggregating these items (externalizing and internalizing) or totaling all items at 48 months in adjusted models.
Tronnes et al. 2020	Five CBCL items were assessed, with 2 aggregated subscales to measure externalizing and with 3 aggregated subscales to measure internalizing. Only one significant association for internalizing problems was reported for acetaminophen use in all three trimesters. No association was reported for one trimester or two trimesters of use.
Sznajder et al. 2020	Significant association for two of seven CBCL items assessed (attention problems aOR 1.23, 95% CI 1.01, 1.51); (aggressive behavior aOR 1.21, 95% CI 1.01, 1.45).

As for the SDQ, different items were analyzed and presented in the seven studies that used this tool. While the conclusions for each study may correctly indicate that a statistically significant association was present for at least one of the items, the results across studies remain inconsistent. This is clearly demonstrated in comparing the results for "total difficulties" from the seven studies that used the SDQ, as summarized in the table below:

Strengths and Difficulties Questionnaire Total Difficulties

Study	Results
Liew et al. 2014	Statistically significant association at age 7 (aRR = 1.13, 95% CI 1.01, 1.27).
Thompson et al. 2014	No statistically significant association for parent-report at age 11 (Multivariable differences in score (MVDS) = 0.8, 95% CI 0.1, 1.8). Statistically significant association for SDQ scores for parent-report at age 7 (MVDS = 1.1, 95% CI 0.2, 2.0) and child report at age 11 (MVDS = 1.1, 95% CI 0.2, 2.0).
Stergiakouli et al. 2016	No statistically significant association for exposure 18 weeks of pregnancy (aRR = 1.01, 95% CI 0.79, 1.27). Statistically significant association present for use at 32 weeks of pregnancy (aRR = 1.37, 95% CI 1.07, 1.75).
Tovo-Rodrigues et al. 2018	No statistically significant association. (6 years old OR = 1.15, 95% CI 0. 88, 1.50; 11 years old OR = 1.19, 95% CI 0.94, 1.50).
Rifas-Shiman et al. 2020	Statistically significant associations present for parent-report (β 0.24, 95% CI 0.02, 0.46) and teacher-report (β 0.35, 95% CI 0.05, 0.65).
Inoue et al. 2021	For parent-report, statistically significant association was only present for any 2 trimesters of use (aRR = 1.22, 95% CI 1.03, 1.45), but the results were not statistically significant for 1st trimester (aRR = 1.08, 95% CI 0.89, 1.31), 2nd trimester (aRR = 0.91, 95% CI 0.69, 1.21), or 3rd trimester (aRR = 1.06, 95% CI 0.86, 1.31), or for all three trimesters (aRR = 1.20, 95% CI 0.98, 1.46). For child-report, statistically significant association was reported in 1st trimester (aRR = 1.50, 95% CI 1.19, 1.88) and 3rd trimester (aRR = 1.33, 95% CI 1.03, 1.71), as well as all 3 trimesters (aRR = 1.53, 95% CI 1.19, 1.96). The reported association was not statistically significant for 2nd trimester (aRR = 1.09, 95% CI 0.78, 1.53) nor for any 2 trimesters (aRR = 1.17, 95% CI 0.94, 1.46).

For all of these reasons, the consistency factor is not satisfied.

3. Specificity Of The Association Is Not Satisfied

As noted above, causality is more likely if an exposure is associated with a specific disease and not with a wide variety of conditions. Drs. Baccarelli and Cabrera both state that this criterion is not satisfied, and I agree.

4. Dose-Response Cannot Be Established From The Epidemiological Data

The dose-response consideration of Bradford Hill is also not satisfied.

As noted above, dose-response is difficult to assess because the observational studies did not control the dosage of acetaminophen taken by pregnant women, and incomplete dosage information was often gathered. Thus, the six studies that analyzed exposure to acetaminophen through maternal use and ADHD diagnosis in children were unable to conduct a proper analysis of dose-response relationships. Instead, these studies attempted to extrapolate dose through various methods, such as total days of use, total weeks of use, the trimesters of use, or tertiles based on acetaminophen or metabolite rates.[242] Because such information does not produce accurate data on maternal dose, these studies do not provide reliable evidence of a dose-response relationship.

The most recent study using data from the Norwegian Birth Cohort, Gustavson et al. 2021, found no dose-response relationship between maternal acetaminophen use and an increased risk of ADHD. To the contrary, Gustavson reported an attenuation of the association for over 29 days of use of acetaminophen (the highest dose available in the data used in this study) after performing

[242] Baker BH, Lugo-Candelas C, Wu H, et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity. JAMA Pediatr. 2020;174(11):1073-1081. doi:10.1001/jamapediatrics.2020.3080.

Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. Brain Sci. 2018;8(127):15. doi:doi:10.3390/brainsci8070127.

Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. JAMA Psychiatry. 2020;77(2):180. doi:10.1001/jamapsychiatry.2019.3259.

Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

Gustavson K, Ystrom E, Ask H, et al. Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder – a longitudinal sibling control study. JCPP Adv. 2021;1(2). doi:10.1002/jcv2.12020.

Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

the sibling control adjustment.[243] Notably, Dr. Baccarelli does not mention this study when discussing dose-response. Instead, the only study from the Norwegian Birth Cohort that Dr. Baccarelli references is a previous study by several of the same investigators, Ystrom et al. 2017.[244]

Although some studies purport to identify a dose response, those studies' inability to properly adjust for relevant confounders is compounded in the group of women who are reported to use the most acetaminophen during pregnancy. As I previously discussed in Section VI.C.4. above, women who use acetaminophen during pregnancy, as a whole, have higher rates of depression and anxiety, more comorbidities, and are more likely to engage in impulsive behaviors than women that do not use acetaminophen during pregnancy. These differences in characteristics are further exacerbated when comparing the highest users of acetaminophen during pregnancy.

Corroborating data has also been reported in various cohorts.[245] By way of example, the data in the table below from Brandlistuen et al. 2013 report an increase in maternal smoking, alcohol consumption, and depression as maternal acetaminophen usage increases.

Maternal Characteristic	No Use % of women	< 28 days of use % of women (% increase)	> 28 days of use % of women (% increase)
Smoking (daily)	2.4%	3.3%	4.3%
Alcohol (> once a week)	3.4%	3.6%	4.4%
Depression	7.5%	9.9%	15.0%

[243] Gustavson K, Ystrom E, Ask H, et al. Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder – a longitudinal sibling control study. JCPP Adv. 2021;1(2). doi:10.1002/jcv2.12020.

[244] Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

[245] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol. 2013;42(6):1702-1713. doi:10.1093/ije/dyt183.

Rifas-Shiman SL, Cardenas A, Hivert M, Tiemeier H, Bertoldi AD, Oken E. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. Paediatr Perinat Epidemiol. 2020;34(3):287-298. doi:10.1111/ppe.12596.

Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res Off J Int Soc Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591.

The only study that performed a dose-response calculation with actual information on dose was Chen et al. 2019. While the exposure data did have some limitations (obtained from insurance records), an analysis of cumulative doses of acetaminophen exposure in the second trimester (OR = 1.13; 95% CI, 0.76–1.69) or in both first and second trimesters (OR = 0.98; 95% CI, 0.50–1.91) were not related to the ADHD risk. Accordingly, the authors determined that the study failed to identify a dose-dependent relationship.

For all of these reasons, the dose-response factor of Bradford Hill is not satisfied.

5. Temporality (Time-Order) Is Inconclusive

Temporality is not satisfied because it is not certain that the hypothesized cause (maternal acetaminophen use) precedes the effect (development of ADHD) in time. As noted above, time-order is difficult to determine in disorders with variable or uncertain time of onset or diagnosis, such as ADHD. To establish time-order in prenatal acetaminophen exposure and development of ADHD, we need to know both the timing of onset of ADHD and the timing of exposure relative to that onset, but neither is known with certainty. Research still has not established the most vulnerable period of fetal brain development for ADHD. As a result, researchers have attempted to cover all three trimesters of pregnancy in the studies to cover timing of exposure relative to the onset of ADHD. Despite this effort, tying exposure of acetaminophen to any specific trimester, much less any particular week of pregnancy, is challenging because of the reliance on maternal recall when gathering data and the potential inaccuracies and bias inherent with data collected based on recollection.

With respect to the studies that used biological measurements to demonstrate exposure, these one-time measurements make it virtually impossible to establish time-order. As previously stated, the biological measurement of acetaminophen levels in cord blood documented in Ji et al. 2018 and Ji et al. 2020 occurred after delivery and, due to the half-life of acetaminophen, is only a measurement of acetaminophen use in the final 1.5-3 hours of pregnancy. Similarly, for Baker et al. 2020, the meconium analyzed may contain acetaminophen from postnatal exposure. As such, the exposures in these studies based on biological measurements may not have any relevance to offspring ADHD development at all.

Because of the uncertainty with the timing of onset of ADHD relative to the timing of exposure, there is insufficient data to satisfy this criterion.

6. The Epidemiological Data Lack Coherence

The available data also lack coherence. Recent studies have determined that the prevalence of ADHD is not increasing.[246] In a meta-analysis of over 100 epidemiologic studies, it was estimated that the worldwide prevalence of ADHD in children and adolescents was 5.3% (95% CI 5.01, 5.56). The study concluded that the prevalence of ADHD did not significantly differ among countries in Europe, Asia, Africa, Australia, and the Americas from the 1985 through 2012. Notably, while the prevalence of ADHD does not differ by country, the reported rates of acetaminophen use during pregnancy does differ.

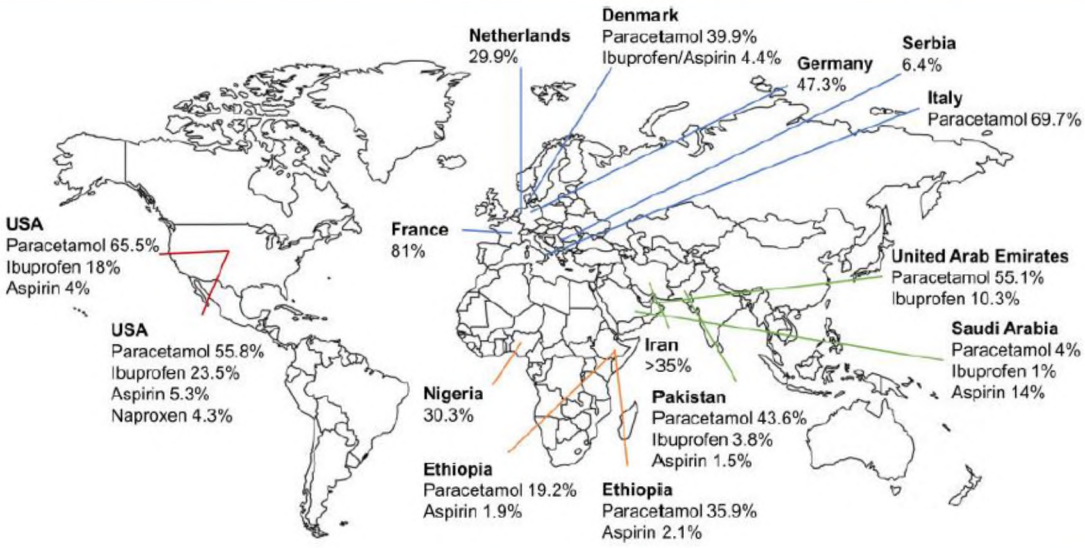

Figure 1. Prevalence of analgesics consumption during pregnancy from different parts of the world. Percentages summarized here are as reported by the literature. More details on each study can be found in Table I and in the text. [247]

If a change in ADHD prevalence rates can be caused by acetaminophen use during pregnancy, as plaintiffs' experts claim, then the prevalence rates of ADHD would be expected to differ among countries with different rates of acetaminophen use during pregnancy. They do not.

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[246] Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol. 2014 Apr;43(2):434-42. doi: 10.1093/ije/dyt261. Epub 2014 Jan 24. PMID: 24464188; PMCID: PMC4817588.

See Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention deficit/hyperactivity disorder: a systematic review and metaanalysis. Pediatrics. 2015;135(4):e994–e1001.

[247] Zafeiri A, Mitchell RT, Hay DC, Fowler PA. Over-the-counter analgesics during pregnancy: a comprehensive review of global prevalence and offspring safety. Hum Reprod Update. 2021 Jan 4;27(1):67-95. doi: 10.1093/humupd/dmaa042. PMID: 33118024.

7. No Experimental Evidence Exists

The experimental evidence factor of the Bradford Hill analysis is not satisfied with respect to maternal acetaminophen use and ADHD in offspring because experimental evidence is not obtainable. As plaintiffs' experts agree, it is unethical to perform experimental studies on pregnant women. Moreover, animal studies provide little insight regarding the development of ADHD in humans due to the significant differences in the size and complexity of the rat versus the human brain, and the fact that ADHD affects complex cognitive and social behaviors that rats do not exhibit. In addition, it is recognized that experimental evidence can include evidence from epidemiologic studies documenting a reduction in risk with removal of exposure, but there is no evidence that reducing acetaminophen use during pregnancy limits or decreases the association with ADHD.

8. Analogy Is Not Satisfied Because No Evidence Exists Of An Analogous Exposure And Outcome

As set forth in more detail in Section VI.C.8, above, I agree with Dr. Baccarelli that very little weight should be placed on the criterion of analogy factor but disagree that there is any evidence that valproic acid is analogous to acetaminophen in terms of its impact of neurodevelopment conditions such as ADHD.

9. Biological Plausibility Is Not Satisfied Because The Biological Mechanisms are Hypothetical

The final Bradford Hill criterion—biological plausibility—also is not met because the reported weak association between maternal acetaminophen exposure and ADHD in offspring does not fit with other biological knowledge regarding the disorder.

While I leave a detailed mechanistic discussion to experts more versed in this area, all of the potential mechanisms that plaintiffs' experts list as potentially explaining the means by which acetaminophen exposure during pregnancy causes ADHD in offspring—such as oxidative stress, epigenetic effects, excess NAPQI formation, effects on the prostaglandin system, endocannabinoid dysfunction, endocrine dysfunction, and altered brain-derived neurotrophic factor—are entirely hypothetical. There is currently no definitive description of any pathologic mechanism that explains the onset and symptoms of ADHD, and plaintiffs' experts' reliance on animal studies in an attempt to validate their hypothetical theories regarding these purported biological mechanisms is inappropriate given the significant differences between the rat and human brain, especially with

respect to the parts of the brain that control the high-level cognitive processes implicated by ADHD.

* * *

For all of these reasons, an analysis under Bradford Hill does not support a causal link between maternal use of acetaminophen during pregnancy and the development of ADHD in offspring.

VIII. THE BAUER "CONSENSUS" STATEMENT DOES NOT SUPPORT A CAUSAL INFERENCE

Dr. Baccarelli relies upon Dr. Ann Bauer's so-called "consensus" statement: *Paracetamol use during pregnancy—a call for precautionary action* in his expert report. This is not a systematic review or pooled study. The article presents no new data or analysis beyond what the underlying studies and meta-analyses previously provided. Moreover, it expressly disclaims a causal conclusion. The Bauer authors could not be more clear: "We agree that limitations and uncertainties remain despite the large body of available data, therefore, we avoided any inference of causality in our [c]onsensus [s]tatement."[248] Their conclusion, in other words, was expressly not one of causation but rather "precaution[]" in light of the equivocal nature of the available data. Bauer et al.'s principal call to action is for "a focused research effort" in an attempt to further evaluate the limitations of the existing literature: "confounding by indication for use"; failure to "control for genetic factors"; inaccurate measures of "exposure and outcome"; and inadequate data concerning "timing, dosage and duration of exposure both prenatally and postnatally."[249] In short, Bauer et al. acknowledges all of the limitations in the data—and the barrier they present to reaching a causal conclusion—that are discussed in detail in this report.

Dr. Baccarelli seems to infer a causal conclusion from Bauer et al.'s secondary call to action—that pregnant women be advised as follows: not to use acetaminophen "unless medically indicated"; to "consult with their physician or pharmacist if they are uncertain whether use is

[248] Bauer AZ, Swan SH, Kriebel D, et al. Reply to 'Paracetamol use in pregnancy — caution over causal inference from available data'; 'Handle with care — interpretation, synthesis and dissemination of data on paracetamol in pregnancy.' Nat Rev Endocrinol. 2022;18(3):192-192. doi:10.1038/s41574- 021-00610-1.

[249] Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy — a call for precautionary action. Nat Rev Endocrinol. 2021;17(12):757-766. doi:10.1038/s41574-021-00553-7.

indicated"; and to "use the lowest effective APAP dose for the shortest possible time."[250] However, all of these admonitions reflect what is already best practice. With any medication, a patient should limit use to appropriate indications and should use the lowest effective dose. Moreover, in the United States, pregnant women are advised by warnings on medications containing acetaminophen that they should "ask a health professional before use." Bauer et al. appear to believe that, at least in some parts of the world, these best practices are not currently being followed. But that belief does not suggest that the authors have concluded that a true causal relationship has been established, a conclusion that (if she held it, contrary to her own express disclaimer of reaching such a conclusion) presumably would have prompted a different, more strongly worded proposed message for pregnant mothers. Thus, put in proper perspective, the Bauer statement adds little to the existing body of literature.

Further, the Bauer statement lacks methodological rigor even as to the conclusion it does purport to reach (which, again, does not establish causation). The statement contains a "Methods" section, but reports only a strategy for searching the literature and revising drafts—not for analyzing the data presented and deriving conclusions from it. The statement merely summarizes at a very high level the findings that the authors believe to be important. The discussion of "neurodevelopmental defects" includes ADHD, ASD and a disparate array of other outcomes, including "language delays, decreased IQ, cerebral palsy, oppositional-defiant disorder, decreased executive function and conduct disorders."[251] This gives no regard to the possibility of distinct etiologies for these disorders. As such, the consensus statement does not add to the epidemiologic evidence in any way.

IX. THE NAVIGATION GUIDE IS NOT A VALID METHODOLOGY AS PLAINTIFFS' EXPERTS APPLY IT HERE

In addition to the standard Bradford Hill methodology typically employed by epidemiologists to evaluate a hypothesis of causation, Dr. Baccarelli also used the "Navigation Guide" method to assess any purported connection between acetaminophen and ADHD or ASD.[252] Dr. Baccarelli states that the Navigation Guide method is "commonly used" and "has been

[250] Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy — a call for precautionary action. Nat Rev Endocrinol. 2021;17(12):757-766. doi:10.1038/s41574-021-00553-7.

[251] Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy — a call for precautionary action. Nat Rev Endocrinol. 2021;17(12):757-766. doi:10.1038/s41574-021-00553-7.

[252] Baccarelli Rep. at 2-3.

recommended by the EPA to assess causal relationships for toxic substances, provides a systematic and rigorous approach to synthesizing evidence, and was established to more readily evaluate causal relationships for toxic and environmental harms."[253] However, the Navigation Guide was not designed to be used by epidemiologists to evaluate a causation connection between an exposure and an outcome.

The Navigation Guide was developed in 2009 by UCSF's Program on Reproductive Health and the Environment.[254] One stated justification for creating the Navigation Guide was because of "differences between environmental and clinical health sciences related to the evidence base and decision context, systematic review methodologies used in the clinical sciences were not seamlessly applicable to environmental exposures."[255] The goal of the Navigation Guide is to establish a systematic and transparent method of research synthesis in environmental health and to "support development of prevention-oriented guidelines for use in clinical settings."[256] Critically, the Navigation Guide is founded on an assumption that environmental exposures differ from clinical interventions in that environmental exposures "are mostly not directed towards improving health" and thus implicate a different risk-benefit calculus[257]—i.e., a precautionary approach, implying a lower threshold to adopting guidelines against exposure (even short of a true causal conclusion), that is aimed toward regulators and authors of prevention guidelines.[258]

Such a framework is a poor fit for assessing whether prenatal acetaminophen use causes ASD or ADHD. There is no dispute that there are benefits to acetaminophen use—including during pregnancy—that must be accounted for in any risk-benefit analysis, which differentiates

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[253] Baccarelli Rep. at 3.

[254] Woodruff TJ, Sutton P; Navigation Guide Work Group. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health Aff (Millwood). 2011 May;30(5):931-7. doi: 10.1377/hlthaff.2010.1219. PMID: 21555477; PMCID: PMC6663095.

[255] Woodruff TJ, Sutton P. The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. Environ Health Perspect. 2014;122(10):1007-1014. doi:10.1289/ehp.1307175.

[256] Woodruff TJ, Sutton P. The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. Environ Health Perspect. 2014;122(10):1007-1014. doi:10.1289/ehp.1307175.

[257] Woodruff TJ, Sutton P. The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. Environ Health Perspect. 2014;122(10):1007-1014. doi:10.1289/ehp.1307175.

[258] Woodruff TJ, Sutton P. The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. Environ Health Perspect. 2014;122(10):1007-1014. doi:10.1289/ehp.1307175.

this kind of exposure from the environmental exposures that are the focus of the Navigation Guide. Ignoring these benefits risks depriving mothers of medical interventions they need. A methodology that focuses solely on potential risk and omits consideration of confounders is prone to mislead.

The Navigation Guide has not been used to establish causation between exposures and ASD or ADHD. Furthermore, I am not aware of practicing epidemiologists who use the Navigation Guide methodology to evaluate the risks associated with ASD or ADHD.

The opinions expressed throughout this report are mine and are reached to a reasonable degree of medical and scientific certainty. I base my opinions on my education, training, professional experience, and on my review of published literature cited in this report or listed on the Materials Considered List, which accompanies my report. I have used the same level of intellectual rigor in preparing this report as I do in my academic research and teaching activities. I reserve the right to add to or amend my opinions if new information or records become available, and to further respond to plaintiffs' experts' opinions.

I will review additional data and information on this matter as they become available.

Jennifer A. Pinto-Martin, Ph.D., M.P.H.

July 21, 2023